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EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/078,225	HENDRIX ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,24,26,29-40 and 42-90* is/are pending in the application.

4a) Of the above claim(s) *23,25,27,28 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,45,46 and 56-59* is/are rejected.

7)☒ Claim(s) *2-22,24,26,29-40,42-44,47-55,60-90* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Because applicants did not distinctly and specifically point out the supposed errors in the restriction/election requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Applicants have elected invention of Group III, claims (in part) 1-22,24,26,29-39,40,42-44,45-90 drawn to compounds, compositions, method of use, and the first recited process of making compounds for the generic Formula (I) wherein components A = Nitrogen; integer n = 1; Y = zero i.e. forming 6-membered saturated 1,4-diazine = piperazine core, and have also elected species of final compound (= AVE 1734) of scheme in Example 34 on page 122 as described in claim 28. Claims 23,25,27,28,41 and subject matter other than meanings of variables as stated earlier are withdrawn from further consideration by the examiner as the same consists of non-elected subject matter. See 37 CFR 1.142(b). Since claims 1-22,24,26,29-39,40,42-44,45-90 link with other inventions, this application will be examined bearing in mind the subject matter as elected by the applicants only.

The restriction election is considered proper, and is now made FINAL.

First action on merits follows.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim1, 45, 46 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A). Claim 1 recites option h) for R component on page 300 wherein valence of N atom is incomplete. Correction is required.

(B). Claim 1 recited option t) for component R2 in poage308 wherein valence of N atom is incomplete. Correction is required.

(C). Claim 1 recites R96 component in page 311, wherein valence of N atom is incomplete. Correction is required.

(D). Claims recite R1 & R2 components with a figure of option (10) e.g. in pages 347 with N atom wherein the valence is incomplete. Correction is required.

(E). Claim 59 recited: " one or more of the atoms contained therein is a radionuclide". It is exactly and definitely not clear as to which carbon atom, or which heteroatoms. The exact site, number of atoms, nature of chemical molecule is more than as recited for claim 1 which consists of pages 299 to 327. The terms "contained" and " one or more" for any compounds as recited in a generic Formula I of claim 1 are not acceptable.

(F). Claims 56-59 recite: " A method for providing a long acting antipsychotic effect...". It is not exactly very clear as to " long acting". How long is long? Is it 1 hr or 24 or 30 hrs?

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 45-49,56-58,67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cardiovascular regulation of arterial pressure, does not reasonably provide enablement for treating conditions or disorders of the central nervous system. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are related to for use in therapy of a patient who may be human being or an animal and therapy is not only directed towards treating a single disorder or condition related to a method of modulating the activity of dopamine D3 receptors, but also towards CNS conditions e.g. schizophrenia, Psychotic Disorders, Substance Dependence, Substance Abuse, Dementia, Dyskinetic disorders in general, and disorders or diseases yet to be discovered.

(1). In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

(2). "Pharmaceutical compositions, depot pharmaceutical compositions and complex combination compositions consisting of a compound(s) of claim1 with one or more dopamine D1, D2, D4, D5, or 5HT receptor antagonists "as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carbocyclic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its composition in combination with other pharmacologically active compounds and pharmaceutically acceptable carrier".

Applicants provide no reasonable assurance that any and all compositions of the instant compounds and their combinations either alone or in a combination therapy as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art; ***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

The claims are drawn to compounds, compositions, method of making, and method(s) (but not limited to a one definite disease) for their generic use for treating conditions or diseases as outlined earlier.

1). The nature of the invention: The compounds and their method of use claim(s) are drawn in part to use them for the treatment of conditions or diseases disorders caused by dopamine D3 receptor-related in a generic way.

2). The state of prior art: There are no known compounds of similar structure (i.e. compounds of invention of Group (III) which have been demonstrated for the treatment of disorders or conditions caused by receptors related to dopamine D3 activity in a generic way.

3). The predictability or lack thereof in the art: It is presumed in the use for subject(s) who are animals suffering from disorders or disease caused by dopamine D3-related disorders as claimed herein, there is a way of identifying those patient(s) who may develop any kind of physiological conditions including (but not limited to) a single disease. There is no evidence of record, which would enable the skilled artisan in the identification of the subject(s) who have the potential of becoming afflicted with the physiological conditions related to dopamine D3 receptor activity as claimed herein.

4). The amount of direction or guidance present and 5).: The presence or absence of working examples: There are no doses present to direct one to protect a potential host from a dopamine D3-related disorder or condition(s), and other multiples of physiologically related condition(s) of various types.

6). The breadth of the claims: The claims are drawn to physiological conditions (not limited to) for treatment of disorder or condition(s) caused by a dopamine D3 receptor activity which are not related and whose treatment(s) is unknown by compound of instant invention.

7). **The quantity of experimentation** need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Discussion about Dementias:

There are no known compounds of similar structure which have been demonstrated to treat dementia of generic nature which is caused by e.g. Alzheimer's disease or depression or CNS infections nor is there any compound that can be used to treat excess dietary alcohol intake, CNS conditions, Psychotic Disorders, Substance Dependence, Substance Abuse, Dementia, Dyskinetic disorders in general, and other diseases by a single compound. For example, the notion that a compound could be effective against chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances" generally. That is because "chemical substance/alcohol abuse or withdrawal caused by the cessation of intake of chemical substances" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat chemical addictions generally have thus failed. Alzheimer's disease is treated, albeit not successfully, using acetylcholine esterase inhibitors and Parkinson's disease using dopamine receptors. A disease in the central or peripheral system is not a single disease but embraces disease that are not related or even "opposites".

Following references are cited to show the present state of art(s):

- Cecil's Textbook of Medicine, vol2, 20th Edn. (see pages1992-1996) for AD related Dementia, and in particularly Table 400-1 listing The most frequent causes of progressive dementia in page 1992.

. ***Understanding about Alzheimer's disease:***

Coyle et al(Science Vol.219, pages 1184-1190(1983)) cites in the summary that:" These cholinergic neurons provide widespread innervation of the cerebral cortex and related structures and appear to play an important role in cognitive functions, especially memory". The authors conclude (see page 1189) that:" The identification of a transmitter-specific pathway selectively affected in a major form of dementia is an important step in the design of diagnostic studies, investigations of pathogenic mechanisms, and the development of therapeutic approaches to these debilitating neuropsychiatric disorders".

- ***Characterization of neurobiological theories of addiction:***

Lingford-Huges AR et al (PubMed Abstract 12697627, also cited as Br. Med. Bull., 65. 209-22(2003)) states that:" The neurochemistry of addiction, particularly involving dopamine, serotonine, opiate and GABA, has been studied with PET and SPECT and similarities between all drugs of abuse have been found such as reduced popaminergic markers. The evidence derived from these advances in neuroimaging **is likely** to herald the emergence of new biological treatments in this important field".

- **Hypothesis related to Opioid modulation of taste hedonics with the ventral striatum:**

Kelley et al (PubMed Abstract 12117573, also cited as Physiol Behav., 76/3,389-95(2002)) state that:" We hypothesize that opoid-mediated mechanisms within ventral striatal medium spiny neurons mediate the affective or hedonic response to food ('liking' or food 'pleasure'). Further refinement of this hypothesis is that activation of ventral striatal opioid..specifically encoded positive affect induced by tasty and or calorically sense food (such as sugar and fat), and promotes behaviors associated with this enhanced palatability".

- **Role of 5HT6 receptor in the rat Brain:**

Bourson et al (J. Pharmac. & Expt. Ther.274, 173-180(1995) state that: " Recently, however, a number of new receptors have been identified via cloning techniques, e.g. 5HT5A, 5HT6B, 5HT6 and 5HT7 receptors.... Relatively little is known about the expression and function of the 5HT5 and 5HT6 receptors in the rat brain". See starting paragraph in page 173.

Applicants recite in claim 48 a combination therapy by using 5HT receptor antagonists in general, and there is no support for using the therapy for human beings as claim herein in the specification.

- **Relation between selective binding of D2/D3 dopamine receptors and atypical antipsychotic effect**:

Bressan et al (PubMed Abstract 12900302, also cited as Am. J. Psychiatry, 160/8,1413-20(2003)) state that:" This finding suggests that modest striatal D2 receptor occupancy and preferential occupancy of limbic cortical dopamine D2/D3 receptors may

be sufficient to explain the therapeutic efficacy and low extrapyramidal symptom profile of atypical antipsychotic drugs, without the need for 5-HT2A receptor antagonism".

- **Inhibition of cocaine-seeking behavior and the role of dopamine D3/D4 receptors:**

Campiani et al (PubMed Abstract 12930145, also cited as J. Med. Chem., 46/18,3822-39(2003)) state that:" Although brain uptake studies are needed to establish whether the compounds achieve brain concentrations comparable to those active in vitro on the D3 receptor, our experiments suggest that antagonism at D2 receptors might significantly contribute to the reduction of cocaine craving by partial D3 agonists".

In the specification (see pages 56-75, and Table 2 in pages 223-298), applicants have tried to describe some sort of prior art(s), and assay/testing methods. The results can be summarized in as:

- In Table on pages 223-298, applicants have included results for D3Ki (nM) for compounds, which have a range from 0.1 to 819 reported as Ki (nM).

Applicants' attention is brought to the fact that the various values reported for above stated test(s) are without involving clinical trials. Applicants have tried to list certain efficacy values obtained by a certain assay method(s), which just indicates a preliminary screening of the compounds prepared.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

In view of the extreme difficulties that have been and are still being encountered in the treatment of CNS conditions, Dementia, Psychotic disorders and diseases yet to be discovered, such utilities are unbelievable on their face and therefore they must be supported by sufficient evidence demonstrating such utilities. There remains the fact that a single compound, which acts not only for treatment of conditions but also for diseases related to activity of dopamine D3 receptor, is generally unprecedented. When efforts toward a goal have persistently failed, it is proper for the PTO to require evidence of such a revolutionary result (in re Ferens, 163 USPQ 609). Such evidence cannot possible demonstrate effectiveness generally.

Claim Objections

5. Claims 2-22,24,26,29-40,42-44,47-55,60-90 is objected to because of the following informalities: The claims are dependent on rejected base claims. Appropriate correction is required.

Conclusion

Allowable Subject Matter

6. The following is a statement of reasons for the indication of allowable subject matter: Claims 1-22,24,26,29-39,40,42,43,44, 50-60, 63-66, 68-90 related to compounds and composition related to invention of Group III subject matter only, would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph and others, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

7. The closest prior arts of ref. New et al (U.S.P. 5116970) teaches Psychotropic heterobicycloalkylpiperazine derivatives. See compounds of Table 1 in columns 1318 and claim 1 with a Formula I. The ref. '970 differ from the instant claims by not having 5:5-membered fused hetero ring connected to 1,4-diazine core.

The other ref. Haadsman-Svensson et al (U.S.P. 5708018) teaches 2-aminoindans as selective Dopamine D3 ligands. The ref. differs from the instant claims by not having 1,4-diazine core.

8. The references either alone or in combination do not indicate or suggest to arrive at a core:

" Fused 5:5-Heterobicycle-piperazine-alkylene-cycloalkyl-CO-NH-carbocycle".

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

JOHN M. FORD
PRIMARY EXAMINER
GROUP - ART UNIT 1624

Sudhaker B.Patel, D.Sc.Tech.
September 26, 2003.

MUKUND SHAH
SUPERVISORY PATENT EXAMINER
ART UNIT 1624